Remarks

Status of the Claims and Support for the Amendments

By the foregoing amendments, claims 57, 69, 70, 73, 74, 77 and 78 are sought to be amended, and new claims 79-175 are sought to be added. Support for the amendment to the claims and for new claims 79-175 can be found throughout the present specification. Therefore, these amendments introduce no new matter.

Upon entry of the foregoing amendments, claims 57, 59-64 and 66-175 are pending in the application, with claims 57, 66, 70, 93 and 137 being the independent claims.

Summary of the Office Action

In the Office Action dated January 27, 2005, the Examiner has made seven rejections of the claims. Based on the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding rejections and that they be withdrawn.

The Rejection Under 35 U.S.C. § 102(b) Over Ogawa

In the Office Action at pages 2-3, section 2, the Examiner has rejected claims 66, 69-71, 73-74 and 77 under 35 U.S.C. § 102(b) over Ogawa *et al.*, U.S. Patent No. 5,094,854 (hereinafter "Ogawa"). Applicant respectfully traverses this rejection.

The Examiner states that Ogawa discloses a liposome comprising DPPC and DSPC. The Examiner concludes that, since Ogawa's formulations are for the release of the active components above physiologic temperature (between 40-45°C), Ogawa meets the requirements of the present claims. Applicant respectfully disagrees with the Examiner's conclusions.

Present claim 66 (and hence, claims 69 and 77 that depend ultimately therefrom and that are also rejected over Ogawa) recites a liposome, comprising an active agent and a liposome interior defined by a gel-phase bilayer membrane, wherein the gel-phase bilayer has a phase transition temperature of 39 to 45°C, and wherein the gel-phase lipid bilayer membrane comprises a first component which is one or more phospholipids and a second component selected from a variety of surface active agents or the active agent. Present claim 66 also requires, in element (d), that the amount of the second component in the gel-phase lipid bilayer membrane is sufficient to increase a first percentage of active agent released from the liposome at the phase transition temperature of the liposome, compared to a second percentage of active agent released in the absence of the second component.

Applicant respectfully submits that Ogawa does not disclose a liposome comprising a first component and a second component, where the amount of the second component is sufficient to increase a first percentage of active agent released from the liposome at the phase transition temperature, compared to a second percentage of active agent released in the absence of the second component. As the Examiner has stated, Ogawa discloses a liposome comprising a first component (DPPC) and a second component (DSPC). However, Ogawa does not disclose that the second component (DSPC) is present in an amount sufficient to increase a first percentage of active agent released from the liposome at the phase transition temperature of the liposome (i.e., a DPPC:DSPC liposome), compared to a second percentage of active agent released in the absence of the second component (i.e., a liposome comprising only DPPC), as required in present claim 66. Ogawa does not disclose that the addition of DSPC (the second component) to DPPC (the first component) liposomes increases the amount of active agent that is

released at the phase transition of the two-component system compared to liposomes only containing DPPC (i.e., element (d) in present claim 66).

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984). Therefore, Applicant respectfully submits that since Ogawa does not disclose every element of present claim 66, Ogawa does not anticipate the presently claimed invention.

With regard to present claim 70 (and hence, claims 71 and 73-74 that depend ultimately therefrom and are also rejected over Ogawa), Applicant respectfully submits that, as noted above, Ogawa does not disclose a liposome comprising a first component and a second component, wherein the amount of the second component in the gel-phase lipid bilayer membrane is sufficient to increase a first percentage of active agent released from the liposome at the phase transition temperature, compared to a second percentage of active agent released in the absence of the second component, as recited in element (iv) of present claim 70. Therefore, Ogawa cannot, and does not, disclose a method of administering an active agent to a preselected target site in a subject's body comprising administering such a liposome. Therefore, Ogawa does not disclose every element of present claim 70. Hence, in view of *Kalman*, Ogawa does not anticipate the presently claimed invention.

In view of the forgoing remarks, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 66, 69-71, 73-74 and 77 under 35 U.S.C. § 102(b) over Ogawa.

The Rejection Under 35 U.S.C. § 102(b) Over Eibl

In the Office Action at page 3, section 3, the Examiner has rejected claims 66 and 69 under 35 U.S.C. § 102(b) over Eibl *et al.*, U.S. Patent No. 5,626,867 (hereinafter "Eibl"). Applicant respectfully traverses this rejection.

The Examiner contends that Eibl discloses a liposome comprising a first component (DPPC) and a second component (DSPA) that contain a variety of active agents. The Examiner therefore concludes that Eibl anticipates the presently claimed invention. Applicant respectfully disagrees with the Examiner's conclusions.

As noted above, present claim 66 (and hence, claim 69 that depends ultimately therefrom and that is also rejected over Eibl) recites a liposome comprising a first component and a second component, wherein the amount of the second component in the gel-phase lipid bilayer membrane is sufficient to increase a first percentage of active agent released from the liposome at the phase transition temperature, compared to a second percentage of active agent released in the absence of the second component.

Applicant respectfully submits that Eibl does not disclose that the alleged second component (DSPA) is sufficient to increase a first percentage of active agent released from the two-component liposome at the phase transition temperature, compared to a second percentage of active agent released in the absence of the second component, as required in present claim 66. The second component (DSPA) disclosed in Eibl is included in the liposomes to provide a negative excess charge to the liposomes. Eibl does not disclose that the DSPA increases a first percentage of active agent released from the liposomes at the phase transition of the two-component liposome (DPPC:DSPA), compared to a second percentage of active agent released in the absence of the second component. In view of the forgoing remarks, Applicant respectfully

submits that Eibl does not disclose every element of present claim 66. Hence, in view of *Kalman*, Eibl cannot, and does not, anticipate the presently claimed invention. Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 66 and 69 under 35 U.S.C. § 102(b) over Eibl.

The Rejection Under 35 U.S.C. § 102(b) Over Alving

In the Office Action at pages 3-4, section 4, the Examiner has rejected claims 66-69 and 77 under 35 U.S.C. § 102(b) over Alving *et al.*, U.S. Patent No. 4,416,872 (hereinafter "Alving"). Applicant respectfully traverses this rejection.

The Examiner states that Alving discloses liposome formulations containing a first component (DPPC) and a ceramide (second component) and that the liposomes contain a quinoline active agent. The Examiner therefore concludes that Alving anticipates the presently claimed invention. Applicant respectfully disagrees with the Examiner's conclusions.

As noted above, present claim 66 (and hence, claims 67-69 and 77 that depend ultimately therefrom and that are also rejected over Alving) recites a liposome comprising a first component and a second component, wherein the amount of the second component in the gel-phase lipid bilayer membrane is sufficient to increase a first percentage of active agent released from the liposome at the phase transition temperature, compared to a second percentage of active agent released in the absence of the second component.

Applicant respectfully submits that Alving does not disclose that the amount of the second component (a ceramide) is sufficient to increase a first percentage of active agent released from the liposome at the phase transition temperature, compared to a second percentage of active

agent released in the absence of the second component (i.e., a DPPC liposome that does not contain a ceramide), as required in the present claim 66.

In view of the forgoing remarks, Applicant respectfully submits that Alving does not disclose every element of present claim 66. Hence, in view of *Kalman*, Alving cannot, and does not anticipate the presently claimed invention. Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 66-69 and 77 under 35 U.S.C. § 102(b) over Alving.

The Rejection Under 35 U.S.C. § 103(a) Over Hristova In View of Ogawa

In the Office Action at pages 5-6, section 6, the Examiner has rejected claims 66 and 69-71 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Hristova, *et al.*, *Macromolecules 28*:7693-7699 (1995) (hereinafter "Hristova"), in view of Ogawa. Applicant respectfully traverses this rejection.

The Examiner contends that Hristova discloses liposomes containing dipalmitolyphosphatidylcholine (DPPC) and a lysolipid, and discloses the effect of lysolipids in general on gel phase bilayers. The Examiner states that it would have been obvious to use any lysolipid in these liposomes with the expectation of obtaining similar effects on the gel phase bilayers. The Examiner states that Hristova does not disclose specific encapsulated active agents or a method of administration using hyperthermia. The Examiner attempts to cure these defects in Hristova with the disclosure of Ogawa, alleging that it would have been obvious to use the liposomes disclosed in Hristova for the delivery of active agents using hyperthermia, since Ogawa discloses that DPPC liposomes can be used for the delivery of active agents using hyperthermia. Applicant respectfully disagrees with the Examiner's allegations and conclusions.

Hristova is directed to the study of bilayer-to-micelle transitions in liposomes comprising PEGylated lipids. Hristova does not disclose that the addition of lysolipid (or any second component for that matter) to gel phase lipid bilayers (i.e., DPPC) is sufficient to increase a first percentage of active agent released from the liposome at the phase transition temperature, compared to a second percentage of active agent released in the absence of the second component (i.e., only DPPC), as required in the present claims. Simply because Hristova may disclose liposomes that comprise DPPC and a lysolipid, Hristova does not disclose that the lysolipid, or any other second component, is present in an amount sufficient to increase the amount of active agent released from the liposomes as compared to liposomes that only comprise a first component (DPPC), as recited in the present claims. In fact, Hristova does not disclose the release of active agents from liposomes in any manner.

These deficiencies in Hristova are not cured by the disclosure of Ogawa, because, as noted above, Ogawa also does not disclose a liposome comprising a first component and a second component, wherein the amount of the second component in the gel-phase lipid bilayer membrane is sufficient to increase a first percentage of active agent released from the liposome at the phase transition temperature, compared to a second percentage of active agent released in the absence of the second component. Hence, Hristova and Ogawa, alone or in combination, do not render obvious the presently claimed invention.

Furthermore, Applicant respectfully submits that the Examiner has provided no motivation for combining the disclosures of Hristova and Ogawa. There is no mention in Hristova of release of contents from liposomes, or use of liposomes in combination with hyperthermia, or any drug delivery scenario. The ordinarily skilled artisan would have found no motivation to use the liposomes disclosed in Hristova for drug delivery, much less in

combination with hyperthermia, as Hristova is directed to the study of bilayer-to-micelle transitions, not to the release of encapsulated contents using hyperthermia.

In view of the foregoing remarks, Applicant respectfully submits that the disclosures of Hristova and Ogawa, alone or in combination, do not render obvious the presently claimed invention. Hence, the Examiner has not established a *prima facie* case of obviousness, and reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are respectfully requested.

The Rejection Under 35 U.S.C. § 103(a) Over Alving In View of Ogawa

In the Office Action at page 6, section 7, the Examiner has rejected claims 66, 69-75 and 77-78 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Alving in view of Ogawa. Applicant respectfully traverses this rejection.

The Examiner states that Alving does not disclose the use of hyperthermia to release active agents from liposomes. The Examiner therefore relies on the disclosure of Ogawa to cure this deficiency, and concludes that it would have been obvious to use hyperthermia in combination with the liposomes disclosed in Alving, since Ogawa discloses that hyperthermia can be used to release active agents from liposomes. Applicant respectfully disagrees with the Examiner's conclusions.

As discussed above, both Alving and Ogawa do not disclose a liposome comprising a first component and a second component, wherein the amount of the second component in the gel-phase lipid bilayer membrane is sufficient to increase a first percentage of active agent released from the liposome at the phase transition temperature, compared to a second percentage of active agent released in the absence of the second component. The Examiner has pointed to

no disclosure, either within Alving, Ogawa, or the knowledge available to one of ordinary skill in the art, to cure these deficiencies.

In view of the foregoing remarks, Applicant respectfully submits that the disclosures of Alving and Ogawa, alone or in combination, do not render obvious the presently claimed invention. Therefore, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are respectfully requested.

The Rejection Under 35 U.S.C. § 103(a) Over Ogawa, Eibl, Alving and Hristova, In View of Boni or Bracken

In the Office Action at pages 6-7, section 8, the Examiner has rejected claims 57, 60-64 and 76 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Ogawa, Eibl, Alving and Hristova in view of Boni, et al., U.S. Patent No. 5,820,848 (hereinafter "Boni") or Bracken, U.S. Patent No. 5,756,121 (hereinafter "Bracken"). Applicant respectfully traverses this rejection.

The Examiner contends that Ogawa, Eibl, Alving and Hristova disclose the classical method of preparing liposomes. The Examiner states however, that these references do not disclose the loading of an active agent in gel phase lipids that are below their phase transition temperature. The Examiner relies on the disclosures of Boni or Bracken to cure this deficiency.

The Examiner contends that Boni indicates that the temperature of the liposomes can be below the main transition temperature of the lipid during the various methods of preparation disclosed therein. The Examiner also contends that Bracken discloses hydrating liposomes at a temperature below the transition temperature of the lipid mixture. The Examiner states that it would have been obvious to load the liposomes of Ogawa, Eibl or Alving below the transition temperature of the lipid based on the disclosures of Boni or Bracken, and therefore concludes

that the present invention is rendered obvious. Applicant respectfully disagrees with the Examiner's conclusions and the contentions on which they are based.

Applicant respectfully submits that neither Boni nor Bracken disclose a method for loading active agents into liposomes as recited in present claim 57 (and hence, claims 60-64 and 76 that depends ultimately therefrom and that are also rejected). Present claim 57 recites a method for loading active agents into liposomes comprising exposing a gel-phase lipid bilayer to an active agent such that the active agent passes into and through the gel-phase lipid bilayer to load the liposome interior with the active agent. Applicant respectfully submits that neither Boni nor Bracken disclose such a method.

Boni discloses the formation of interdigitated-fusion liposomes. The Examiner indicates that in Example 4 of Boni, the liposomes can be formed below the main transition temperature of the lipid. The relevant portion of Example 4 of Boni states:

> A bioactive agent which does not interact with the lipid is then mixed in with the aqueous solvent used to form the Liposomes . . . . The temperature of the liposomes are below the main phase transition temperature of the lipid. . . .
>
> To form IF liposomes, the gel is incubated at a temperature below the Tm of the lipid for a period ranging from about 1 minute to about 1 hour followed by an incubation period of about 1 minute to about 1.0 hour at a temperature above Tm of the lipid. The inducer is then removed by evaporation, positive nitrogen pressure or dilution . . . . As the inducer is removed, liposomes form, generally varying in size from about 0.25 microns to about 20 microns.

Boni at column 17, lines 25-58. Example 4 does not disclose a method for loading active agents into liposomes comprising exposing a gel-phase lipid bilayer to an active agent such that the active agent *passes into and through* the gel-phase lipid bilayer to load the liposome interior with the active agent, as recited in present claim 57.

The liposome preparation process in Boni employs inducers to generate interdigitated liposomes. As noted in Example 4, while the liposomes are held at a temperature below their main phase transition temperature during a portion of the procedure, in order for the interdigitated liposomes to form, the gel is then incubated for a "period of about 1 minute to about 1.0 hour *at a temperature above the Tm of the lipid*" (emphasis added). As stated in Boni,

> . . . IF liposomes are formed from IF gels when the fluidity of the gels is changed such that a fluid phase lipid bilayer is formed from the gel phase interdigitated bilayer. The interdigitated bilayer generally passes from the gel phase to the fluid phase when the IF gel is incubated *at a temperature above the transition temperatures* ("Tm") of the component lipids of the gel.

Boni at column 11, lines 18-24 (emphasis added). Thus, while a portion of the process may take place while the liposomes are below their main transition temperature, the actual formation process requires the gels to transition from gel phase to fluid phase by incubating the liposomes at a temperature *above* the main transition temperature.

Furthermore, even assuming *arguendo* that the liposome formation process disclosed in Boni could occur below the main transition temperature of the liposomes, Boni does not disclose a method for loading active agents into liposomes comprising exposing a gel-phase lipid bilayer to an active agent such that the active agent *passes into and through* the gel-phase lipid bilayer to load the liposome interior with the active agent, as recited in present claim 57 (and hence, the claims that depend ultimately therefrom). The process disclosed in Boni loads agent into liposomes by forming the liposomes *around* (i.e. encapsulating) the agent. Loading does not occur by exposing the liposomes to an active agent which then *passes into and through* a gel-phase lipid bilayer (i.e. an already formed liposome), as recited in present claim 57.

Therefore, in view of the foregoing remarks, Applicant respectfully submits that the present invention is not rendered obvious by Ogawa, Eibl, Alving, Hristova, or Boni, alone or in combination, as none of these references disclose the loading method of present claim 57 (and therefore the claims that depend ultimately therefrom).

With regard to Bracken, the Examiner is directed to Example 2 of Bracken describing the hydration of liposomes below their transition temperature:

> The powder was collected and combined with amikacin drug solution (as prepared in Example 1).... The solution was placed in a beaker and set in a 40°C water bath and *hydrated* with mixing until the solution reached 40°C (about 25 minutes). The solution was then placed in a homogenizer (Gaulin 15M) for approximately 30 passes at 10,000 psi while maintaining the inlet temperature at 40°C. The resulting solution was filtered through a 0.8 micron nylon filter. The solution was ultrafiltered to replace unencapsulated drug with the new buffer .... Thus a surprising aspect of the present invention is that the *hydration* of liposomes occurred significantly below the transition temperature of the formulation (about 52°C).

Bracken at column 8, line 55 through column 9, line 6 (emphasis added).

Applicant respectfully submits that the ordinarily skilled artisan would readily understand that Bracken does not disclose a method for loading active agents into liposomes comprising *exposing a gel-phase lipid bilayer* to an active agent such that the active agent *passes into and through* the gel-phase lipid bilayer to load the liposome interior with the active agent, as recited in present claim 57 (and hence, the claims that depend ultimately therefrom).

The process disclosed in Bracken is directed to the hydration of a lipid powder with an amikacin containing solution. This hydration process, however, does not result in an active agent passing into and through a gel-phase lipid bilayer. The ordinarily skilled artisan would readily understand that, during lipid hydration from a powder, liposomes form *around* the agent-containing solution as the dried lipid is hydrated. The process therefore results in liposomes with

drug solution both inside (encapsulated) and outside (unencapsulated) the vesicles. Once the liposomes are formed (i.e., a gel-phase lipid bilayer defining a liposome interior is present), there is no indication that active agent is able to pass into a through the gel-phase bilayer to load the liposome interior. Therefore, Bracken does not disclose a method for loading active agents into liposomes comprising exposing a gel-phase lipid bilayer that defines a liposome interior (i.e., formed, hydrated liposomes) to an active agent, *such that the active agent passes into and through the bilayer* to load the liposome interior with the active agent. Therefore, Bracken does not disclose the presently claimed invention.

In view of the foregoing remarks, Applicant respectfully submits that present invention is not rendered obvious by Ogawa, Eibl, Alving, Hristova, Boni, or Bracken, alone, or in combination, as none of these references disclose the loading method of present claim 57 (and therefore the claims that depend ultimately therefrom). Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

The Rejection Under 35 U.S.C. § 103(a) Over Ogawa, Eibl, Alving and Hristova, In View of Boni or Bracken and Further in View of Mayer

In the Office Action at page 7, section 9, the Examiner has rejected claim 59 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Ogawa, Eibl, Alving and Hristova, in view of Boni or Bracken, and further in view of Mayer *et al.*, *Chemistry and Physics of Lipids 40*:333-345 (1986). Applicant respectfully traverses this rejection.

The Examiner states that Ogawa, Eibl, Alving, Hristova, Boni and Bracken do not disclose loading of drugs by a pH gradient. The Examiner relies on the disclose of Mayer to cure this deficiency. The Examiner contends that it would have been obvious to use the pH gradient

loading method disclosed in Mayer to load the liposomes of Ogawa, Eibl, Alving, Hristova, Boni or Bracken, since one can achieve higher trapping efficiencies as disclosed in Mayer. The Examiner therefore concludes that the present invention is rendered obvious. Applicant respectfully disagrees with these conclusions.

Claim 57, from which claim 59 ultimately depends, recites a method for loading active agents into liposomes comprising exposing a gel-phase lipid bilayer to an active agent such that the active agent *passes into and through* the gel-phase lipid bilayer to load the liposome interior. Applicant respectfully submits that, as noted above, neither Ogawa, Eibl, Alving, Hristova, Boni nor Bracken disclose such a loading method, and therefore are deficient references on which to base a *prima facie* case of obviousness. The disclose of Mayer does not cure these deficiencies because Mayer also does not disclose such a loading method. Mayer does not disclose loading gel phase liposomes at temperatures below the phase transition temperature such that an active agent passes into and through the gel-phase lipid bilayer to load the liposome interior with the active agent.

In view of the foregoing remarks, Applicant respectfully submits that present invention is not rendered obvious by Ogawa, Eibl, Alving, Hristova, Boni, Bracken, or Mayer, alone, or in combination, as none of these references disclose the loading method of present claim 57 (and therefore dependent claim 59). Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).